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### A quantitative analysis of antibiotic usage in British sheep flocks

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## A quantitative analysis of antibiotic usage in British sheep flocks

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Abstract:	<p>The aim of this study was to examine the variation in antibiotic usage between 207 commercial sheep flocks using their veterinary practice prescribing records. Mean and median prescribed mass per Population Corrected Unit (mg/PCU) was 11.38 and 5.95 respectively and closely correlated with Animal Defined Daily Dose (ADDD) 1.47(mean), 0.74(median) (<math>R^2 = 0.84</math>, <math>p &lt; 0.001</math>). This is low in comparison with the suggested target (an average across all UK livestock sectors) of 50mg/PCU. In total, 80% of all antibiotic usage occurred in the 39% of flocks where per animal usage was greater than 9.0 mg/PCU. Parenteral antibiotics, principally oxytetracycline, represented 82% of the total prescribed mass, 65.5% of antibiotics (mg/PCU) were prescribed for the treatment of lameness. Oral antibiotics were prescribed to 47% of flocks, 64% of predicted lamb crop/farm. Lowland flocks were prescribed significantly more antibiotics than hill flocks. Variance partitioning apportioned 79% of variation in total antibiotic usage (mg/PCU) to the farm level and 21% to the veterinary practice indicating that veterinary practices have a substantial impact on overall antimicrobial usage. Reducing antibiotic usage in the sheep sector should be possible with better understanding of the drivers of high usage in individual flocks and of veterinary prescribing practices.</p>

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# A quantitative analysis of antibiotic usage in British sheep flocks

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## Abstract

The aim of this study was to examine the variation in antibiotic usage between 207 commercial sheep flocks using their veterinary practice prescribing records. Mean and median prescribed mass per Population Corrected Unit (mg/PCU) was 11.38 and 5.95 respectively and closely correlated with Animal Defined Daily Dose (ADDD) 1.47(mean), 0.74(median) ( $R^2 = 0.84$ ,  $p < 0.001$ ). This is low in

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22 comparison with the suggested target (an average across all UK livestock sectors) of 50mg/PCU. In  
23 total, 80% of all antibiotic usage occurred in the 39% of flocks where per animal usage was greater  
24 than 9.0 mg/PCU. Parenteral antibiotics, principally oxytetracycline, represented 82% of the total  
25 prescribed mass, 65.5% of antibiotics (mg/PCU) were prescribed for the treatment of lameness. Oral  
26 antibiotics were prescribed to 49% of flocks, 64% of predicted lamb crop/farm. Lowland flocks were  
27 prescribed significantly more antibiotics than hill flocks. Variance partitioning apportioned 79% of  
28 variation in total antibiotic usage (mg/PCU) to the farm level and 21% to the veterinary practice  
29 indicating that veterinary practices have a substantial impact on overall antimicrobial usage.  
30 Reducing antibiotic usage in the sheep sector should be possible with better understanding of the  
31 drivers of high usage in individual flocks and of veterinary prescribing practices.

## 32 Introduction

33 Antibiotic usage in farmed species is under scrutiny because of increasing concern surrounding  
34 antimicrobial resistance, with imprudent patterns of prescribing and use representing a potential  
35 risk to human and animal health (O'Neill, 2015).

36 Antibiotic usage is measured across the EU at a national level using the metric of total mass (mg) of  
37 any and all antibiotic active ingredients per Population Corrected Unit (mg/PCU). The PCU  
38 denominator is calculated as a standardised figure for each farmed species for breeding and  
39 slaughtered animals (EMA, 2013). There is significant variation between countries, with the UK's  
40 usage at 62.1 mg/PCU ranked 15th out of 26 EU countries in order of highest antibiotic usage (EMA,  
41 2013).

42 The UK government has identified reducing antibiotic usage as a priority and has adopted the  
43 mg/PCU metric to measure usage across all livestock sectors (UK Government, 2016) with a target  
44 for UK livestock production set at 50mg/PCU. The UK is the 4th largest livestock producer in the EU  
45 as calculated by PCU biomass (EMA, 2013) and the sheep industry in the UK is the largest in the EU.  
46 The sheep sector is also the largest single sector of UK livestock agriculture, representing 40% of the  
47 PCU biomass (EMA, 2013). For this reason, antibiotic usage in the UK sheep industry has a  
48 disproportionate impact on the total mg/PCU figure for the whole UK livestock sector.

49 Species or sector specific targets are also expected to be set (UK Government, 2016), for which a  
50 detailed understanding of current usage patterns is required in order to make informed decisions in  
51 this area. To understand how to reduce antibiotic usage in each sector, we need to understand the  
52 farm level usage, variability between farms within a species and reasons for use within farm.

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53 The aim of this study was to collate information from a large number of British sheep farms,  
54 primarily to evaluate the magnitude and variation in antibiotic usage and secondarily to assess  
55 factors that impact on farm level antibiotic usage.

56 Methodology

58 Farm selection criteria

59 Two hundred and seven anonymised flock records were collated from a convenience sample of eight  
60 veterinary practices that were able to contribute sales and prescription records for all antibiotic  
61 products supplied to a minimum of ten sheep farm enterprises which met specific selection criteria.  
62 Practices were recruited with client farms located in the following regions: West Wales, Mid Wales,  
63 Central Scotland and the following English regions: South West, South East, West Midlands, East  
64 Midlands and North West. Each practice provided details of all antibiotic products and quantity  
65 prescribed to all their sheep farming clients during the study period of August 2015-July 2016 along  
66 with flock level information on breeding flock size, flock type (categorised as Hill (18), Upland (25),  
67 Lowland (164)) and management system (Organic (11), Conventional (196)). A single, recent year  
68 was selected for analysis to reduce recall bias in the recording of the breeding ewe flock size, which  
69 were used as the denominator for antibiotic calculations. Data were requested from farms that  
70 were sheep only holdings with a minimum of 100 breeding ewes; to avoid the risk of antibiotics  
71 being used in other species the study was restricted to farms exclusively with sheep. A minimum  
72 breeding ewe flock size was used to reduce the potential bias associated with unnecessarily large  
73 pack sizes of antibiotic products being supplied for small flocks, where unused product could  
74 represent a large proportion of the purchased total. The threshold also represented a reasonable cut  
75 off for commercial vs leisure/hobby flocks. The flock size ranged from 100 to 4000 ewes, with a  
76 mean and median size of 529 and 300 respectively. The threshold was selected based upon the  
77 maximum number of doses per product unit available in the UK.



## 78 Calculation of antibiotic usage per population correction unit (PCU)

79 The mass of antibiotic active ingredients per PCU was calculated for each prescribed product using  
80 the manufacturer supplied product specification and the ESVAC standard methodology (EMA, 2015)  
81 using approximate average body weights of adults (75kg) and weighted average weight for  
82 slaughtered lambs drawn from the Eurostat census. To calculate the lamb component of the PCU the  
83 mean rearing % of lambs per ewe (143.5%) in the reference period was estimated using the UK levy  
84 board benchmarking data (AHDB 2016) as a coefficient of the standard ESVAC lamb weight value  
85 (20kg). This metric was applied to all flocks in the study.

86 The average ESVAC ewe and lamb weights were considered reasonable estimates for lowland flocks  
87 by the authors, however breeds used in hill farming in UK systems are generally smaller and less  
88 fecund than their lowland counterparts. To account for this potential bias, a sub-analysis was  
89 conducted where a separate 'Hill-PCU' was used as the denominator for antibiotic usage in hill flocks  
90 specifically. This was calculated based on a mature ewe body weight of 55kg, a lamb average body  
91 weight of 16kg and a rearing percentage of 115% (Welsh Farm Survey, 2016).

## 92 Calculation of antibiotic usage by Defined Daily Doses (DDDvet), Defined Course 93 Doses (DCDvet) and Animal-Defined Daily Dose (ADDD).

94 Antibiotic usage at flock level was estimated using standardized methods as follows. The number of  
95 Defined Daily Doses (DDDvet) and Defined Course Doses (DCDvet) as Animal Defined Daily Dose  
96 (ADDD) per farm for the one year reference period were estimated for each farm. The breeding  
97 female population was used as the flock denominator and a standardized body weight of adult  
98 sheep of 75kg and was applied to convert the mg/kgBW into a per head unit in line with the  
99 standardised methodology set out by the ESVAC (EMA/710019/2014)(EMA, 2015). For oral and  
100 parenteral products DDDvet and DCDvet were calculated for each antibiotic product using either; (a)  
101 the licenced recommended maintenance dose for sheep where available, (b) the licenced  
102 recommended maintenance dose for cattle or pigs [dependent on the species licencing of the

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product] where the product used was not licenced for sheep but prescribed under the Veterinary Medicines Directorate ‘cascade’. Topical preparations were excluded from the calculation of DDDvet and DCDvet in line with the ESVAC methodology. All products and preparations, including topical and oral preparations, were included in the mg/PCU metric. The ADDD metric was generated for comparison with mg/PCU and was calculated as previously described (Bos et al., 2013) and used for comparison of antibiotic usage in dairy herds (Kuipers, Koops, & Wemmenhove, 2016). An additional Lamb DCDvet metric was calculated for oral antibiotics licenced exclusively for neonatal lambs where dose was independent of body weight. These products were assigned a lamb DCDvet per animal rather than mg/kg body weight. In this study, the dose rates for these products were calculated on a fixed volume per animal as directed by manufacturer recommendations, rather than mg/kg bodyweight. The number of lamb DCDvet doses was then divided by the breeding ewe population per farm to generate an index of lamb doses per breeding ewe per flock.

Statistical modelling

A Linear regression model was used to assess the correlation between mg/PCU, ADDD (DDDvet and DCDvet) using MiniTab17 (Minitab 17 Inc, 2015). A multivariable regression model was developed with antibiotic use (mg/PCU) as the response variable. A multi-level structure was used to account for correlations in antibiotic use between farms, within a veterinary practice. The number of breeding ewes, farm type (organic, conventional) and farm stratification (Lowland, Upland, Hill) were forced into the model. Based on the a priori hypotheses of this study, all variables were retained in the model. The model was built using MLwiN version 2.36 (Charlton, et al, 2017) and parameter estimates generated using iterative generalised least squares (IGLS). Model fit was assessed by examining q-q plots of residuals. The mg/PCU of antibiotic calculated for each farm were transformed to meet the assumptions of the multivariable regression model. The optimal transformation (mg/PCU to the power 0.28) was calculated using the *boxcox* function in the MASS package in R (Venables, W. N. & Ripley, 2002). Variance partition coefficients (VPCs) were calculated using the final model to evaluate the proportion of unexplained variance occurring at both the farm

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3 129 and veterinary practice level. To facilitate interpretation of the final model, predictions were  
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5 130 calculated by fixing explanatory variables at their mean value except the variable of interest.  
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7 131 Predictions and their corresponding confidence interval estimates were back transformed to the  
8  
9 132 mg/PCU scale.

### 133 Antibiotic use by disease

134 Analysis of the disease for which each antibiotic product was prescribed was possible for 24 flocks  
135 from one practice that routinely and accurately collected this information. Diseases were  
136 categorised for comparison of antibiotic usage by antibiotic class in mg/PCU. Disease incidence rates  
137 were estimated for the two most common prescribed reasons for antibiotic usage, using the DCDvet  
138 metric and the following assumptions: licenced dose rate was used for each dose, 75kg ewe body  
139 weight for each administered dose, all doses administered to ewes not lambs, zero wastage of  
140 antibiotic product.

## 141 Results

### 143 Distribution of total antibiotic usage per farm and comparison of metrics.

144 Flock usage of antibiotics during the reference period ranged from 0 mg/PCU to 116.9 mg/PCU, with  
145 a mean of 11.38 (sd = 15.35) and median of 5.95 (IQR = 2.47 – 13.95) mg/PCU respectively. 4.3%  
146 of flocks recorded no antibiotic prescriptions during the reference period, while 1.9% of flocks  
147 recorded over 50 mg/PCU (Figure 1). In total, 80% of all antibiotic usage occurred in the 39% of  
148 flocks where per animal usage was greater than 9.0 mg/PCU

149 Antibiotic usage at the farm level, using the ADDD metric, calculated using the DDDvet method  
150 indicated mean daily doses per animal of 1.47 (sd = 2.1) and a median of 0.74 (IQR = 0.299 – 1.97).  
151 Mean and median usage as calculated by DCDvet per ewe per flock were 0.39 (sd = 0.53) and 0.20  
152 (IQR = 0.17, 0.26) respectively.

Correlation between mg/PCU and ADDD using DDDvet for farms in this study was  $R^2 = 0.84$  ( $P < 0.001$ ). The correlation between mg/PCU and ADDD using DCDvet was  $R^2 = 0.77$  ( $P < 0.001$ ). There was no significant correlation between Lamb DCDvet and any of the other metrics.

Distribution of antibiotic usage by antibiotic group

The mass of antibiotic products prescribed were ranked by antibiotic class (Table 1). The most commonly prescribed antibiotic was oxytetracycline, which comprised 57.4% of the total, followed by penicillin (including extended spectrum penicillins) 23.7%, aminoglycosides 10.7%, lincomycin 4.7%, macrolides 1.7%, fluoroquinolones 0.5% and florfenicol 0.5%, with the remaining 0.9% being made up of cephalosporins, sulphonamides, trimethoprim and thiamphenicol.

Distribution of antibiotic usage by route of administration

Parenterally administered products represented 84.4% of the total mass used, whilst topical preparations represented 12.3% and oral represented 3.3% of the total mg/PCU (Table 1).

Table 1 Percentage distribution of antibiotic prescriptions by mass (mg/PCU), antibiotic class and administration route per class across all farms.

Antibiotic class	Administration route (% of each class)			% of Total mass of all classes
	Oral	Parenteral	Topical	
Oxytetracycline		91%	9%	57.4%
Penicillin (inc extended spectrum)		98%	2%	23.6%
Aminoglycoside	29%	66%	6%	10.7%
Lincomycin			100%	4.7%
Macrolides		60%	40%	1.7%
Florfenicol		100%		0.5%
Fluoroquinolones		38%	62%	0.5%
Other	25%	55%	21%	0.9%

## 170 Comparison of antibiotic group and route of administration between 1<sup>st</sup> and 4<sup>th</sup>

### 171 quartile (high and low users)

172 A comparison was made between the antibiotic usage of the upper quartile of flocks (Q1) (High  
173 users >13.95mg/PCU) and lower quartile flocks (Q4) (Low users < 2.47 mg/PCU). All the antibiotic  
174 classes were represented in the Q1 group of flocks, however the Q4 group used fewer antibiotic  
175 classes (oxytetracycline, penicillin (including extended spectrum), aminoglycosides, lincomycin). The  
176 total usage of all of these individual classes was significantly lower in Q4 compared to Q1. There was  
177 no significant difference in the proportional usage of antibiotic classes i.e. oxytetracycline was still  
178 the predominant antibiotic used, followed by penicillins, or in administration route.

## 179 Seasonality of antibiotic usage by antibiotic group

180 Antibiotic prescriptions were distributed throughout the year with a significant increase in spring  
181 along with a significant relative increase in the mg/PCU of penicillins and aminoglycosides (Figure 2).  
182 Oxytetracycline usage also increased in the spring but to a lesser extent than the increase observed  
183 with penicillin and the aminoglycosides. February was the only month in which oxytetracycline was  
184 surpassed by penicillins as the most commonly prescribed antibiotic class. All of the oral  
185 aminoglycoside antibiotics (neomycin and spectinomycin) were prescribed during the spring months,  
186 which coincides with the majority of lambing periods in UK flocks.

## 188 Oral antibiotic usage in lambs

189 In this study, 47% (95% CI: 41% - 62%) of flocks used oral antibiotics licenced for  
190 treatment/prophylaxis of colibacillosis in lambs. A further 2% of flocks, (4 farms from 2 practices)  
191 were prescribed oral antibiotic tablets. Of the lowland flocks sampled, 77% (95% CI: 42% - 90%) were  
192 prescribed oral antibiotics, whereas 44% (95% CI: 41% - 69%) of upland flocks and 25% (95% CI: 17%  
193 - 50%) of hill flocks were prescribed oral antibiotics. Licenced oral antibiotic products in this study

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194 were explicitly only approved for use in neonatal lambs. In those flocks using oral antibiotics, the  
195 mean number of lamb oral antibiotic doses prescribed per ewe per flock was 1.23 (95% CI: 0.034,  
196 5.181) and median of 0.92 (95% CI: 0.8, 1.2) doses per ewe per flock.

197 **Topical antibiotic preparations**

198 Topical antibiotic preparations were assigned to one of three categories for comparison of the  
199 percentage prescribed total mass (mg/PCU) across all farms: ophthalmic preparations (4%), aerosol  
200 sprays (45%) and soluble powders (51%). Ophthalmic preparations were prescribed to 22% of farms,  
201 aerosol sprays were prescribed to 47% of farms and soluble powders were prescribed to 7% of  
202 farms. DDDvet and DCDvet metrics were not established for topical preparations in line with EMA  
203 standard methodology.

204 **Farm Stratification**

205 Considerable variation was observed in antibiotic usage between farms both within and between  
206 farm stratification categories (Figure 3). The distributions of mg/PCU within all categories of farm  
207 were positively skewed.

208

209 **Multivariable analysis: Influence of veterinary practice, management system and**  
210 **farm stratification on antibiotic use**

211 Accounting for influence of practice in the multi-level model structure, lowland farms were shown to  
212 use significantly more antibiotics (mg/PCU<sup>0.28</sup>) than hill farms (p=0.02), principally due to higher  
213 usage of parenteral oxytetracycline. When a ‘Hill-PCU’ coefficient (accounting for the lower body  
214 weights and lamb output) was applied to the antibiotic usage of hill flocks as opposed to the  
215 standard PCU coefficient appropriate to lowland flocks, a significantly lower antibiotic usage in hill  
216 flocks was still identified (p = 0.03). There was a non-significant trend for organic farms to use less  
217 antibiotic than conventional farms (p=0.06). In the final model, 21% of the unexplained variation in

218 mg/PCU<sup>0.28</sup> occurred between veterinary practices, with the remaining 79% of variation being  
 219 between farms. Additional detail on model results are provided in supplementary material.

220

## 221 Distribution of antibiotic usage by clinical diagnosis

222 A subset analysis of antibiotic class prescription patterns by clinical diagnosis was conducted on the  
 223 data supplied by one veterinary practice with unusually detailed records of all antibiotics prescribed.  
 224 Analysis of these 24 flocks data revealed that lameness accounted for 65.5% of antibiotics prescribed  
 225 by this practice (Table 2) and oxytetracycline was the most commonly prescribed antibiotic  
 226 accounting for 63.5% of the total, followed by penicillins (26.8% of total). Penicillins were prescribed  
 227 for the widest range of clinical diagnoses (9 of 11 disease categories, Table 2), while oxytetracycline  
 228 was prescribed for 4 of 11 categories and 85.1% of all oxytetracycline was prescribed for treatment  
 229 of lameness (Table 2). The mean proportion of oxytetracycline prescribed for the treatment of  
 230 lameness per farm was 91% (95% CI: 81%, 99%).

231 *Table 2. Antibiotic prescription patterns by diagnosis from a subset of 24 flocks supplied by one veterinary practice with*  
 232 *unusually detailed prescription records. The proportions of antibiotics per class prescribed for each diagnosis are stated as a*  
 233 *percentage of the total prescribed for that antibiotic class. The number of flocks prescribed a given class for a given*  
 234 *diagnosis is stated in brackets. The Lameness category includes Contagious Ovine Digital Dermatitis, Footrot and*  
 235 *Interdigital Dermatitis.*

Treatment Diagnosis	Aminoglycosides	Penicillins (including extended spectrum)	Macrolides	Oxytetracycline	Lincomycin	% Total mg/PCU by cause
Abortion				5.4% (1)		3.2%
Colibacillosis	43.4% (11)					2.2%
Lambing (inc dystocia, prolapse)		29.4% (18)				9.7%
Lameness (inc CODD, FR, ID)	24.6% (1)	34.5% (13)	75.6% (10)	85.1% (23)	100.0% (4)	65.5%

Listeriosis		0.3% (1)				0.1%
Mastitis		10.3% (4)				3.4%
Metritis		0.4% (1)				0.1%
Ophthalmic		1.7% (5)		9.2% (4)		6.0%
Pneumonia		0.4% (1)		0.3% (1)		0.3%
Polyarthritis	32.0% (2)	18.8% (9)	24.4% (4)			8.2%
Not recorded		4.3% (5)				1.4%
% Total mg/PCU by antibiotic class	2.0%	26.8%	6.3%	63.5%	1.3%	

Incidence of lameness treatments and treatments associated with lambing were estimated using the DCDvet for each flock (Table 3). DCDvet based estimates of lameness incidence between farms indicate a wider and higher range of treatment rates for lameness with a median of 29.6 ewe treatment DCDvet per 100 ewes per year.

Table 3 Disease incidence estimates for lameness and lambing associated events based upon prescribed antibiotic DCDvet values for parenteral antibiotics prescribed for each.

	Mean	Median	Range
Parenteral treatments for lameness	42.7 ewe treatment DCDvet per 100 ewes per year	29.6 ewe treatment DCDvet per 100 ewes per year	9.6 – 67.0
Parenteral treatments for lambing associated events (including dystocia, prolapse)	7.8 ewe treatment DCDvet per 100 ewes per year	6.8 ewe treatment DCDvet per 100 ewes per year	3.2 – 10.3

Discussion

The results of this study suggest that antibiotic use in all sectors and management systems of the UK sheep industry is very low in comparison with the overall average of 56mg/PCU recorded across all



248 UK livestock sectors in 2015 (UK government VARSS 2015). The relatively low usage of antibiotics in  
249 the sheep sector should not give rise to complacency. This study highlights a number of areas where  
250 potential improvements in our use and monitoring of antibiotics can be made.

251 If antibiotic usage is to be reduced in line with the stated EU and UK policy statements (UK  
252 Government, 2016) then it would be logical to target those diseases which drive highest usage with a  
253 'Refine, Reduce, Replace' strategy, whilst keeping in mind the other priorities, principally animal  
254 welfare. In identifying the most appropriate strategy for minimising any potential antibiotic  
255 resistance selection risk, the metric used needs to be appropriate. It would be counterproductive if a  
256 targeted adoption of one metric, led inadvertently, to antibiotic use patterns that did not reflect the  
257 best evidence based clinical practice or neglected high risk antibiotic use.

258 It should be noted that the dominance of parenteral oxytetracycline and to a lesser extent penicillins  
259 identified in this study resulted in a close correlation between the two main metrics for antibiotic  
260 usage; Population Corrected Unit (PCU) and Animal Defined Daily Dose ADDD (DCDvet/DDDvet). The  
261 close correlation between mg/PCU and ADDD (DDDvet/DCDvet) in the sheep sector may be very  
262 helpful in simplifying monitoring of antibiotic usage, however the use of oral aminoglycosides in  
263 neonatal lambs and the use of soluble antibiotic powders for topical use in footbaths or hand sprays  
264 to control lameness (particularly contagious ovine digital dermatitis (CODD)) present two important  
265 challenges that may be obscured by the scale of oxytetracycline use. Both of these practices have  
266 the potential to subject a larger proportion of the flock, as well as the wider farm environment, to  
267 antibiotic resistance selection, than targeted individual parenterally administered treatments.

268 Overall, 79% of the variation in antibiotic usage observed between flocks was attributable to  
269 differences between farms. These are likely to include a combination of biological and management  
270 differences, which influence the force of infection and genetic differences in disease susceptibility to  
271 infection. However, the between farm variation in antibiotic use will also likely be influenced by the  
272 priorities, understanding and attitudes of the farmers and shepherds responsible. Previous studies

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273 have demonstrated differences in attitude to population health management between sheep and  
274 pig farmers (Garforth, Bailey, & Tranter, 2013). In the context of antibiotic usage this study has  
275 demonstrated that flock type (Hill, Upland, Lowland) was significantly associated with different  
276 levels of antibiotic use and the basis for these differences warrant further investigation.

277 There was an important further 21% of variation attributable to the veterinary practice serving the  
278 individual flocks after the effects of stratification, region, flock size and management system were  
279 accounted for. This suggests there is an important influence of practice prescribing policy and  
280 practice culture on the quantity of antibiotics prescribed for sheep. Reasons for these differences  
281 cannot be elucidated from the current study and this would be a worthwhile topic for future  
282 research. Surveys that rely on the voluntary contribution of data from participants (veterinary  
283 practices in this case) are subject to bias and it is unclear the extent to which this convenience  
284 sample is representative of the national flock. With the current absence of a universal, robustly  
285 audited, mandatory reporting system of antibiotic use/prescription, these study findings represent  
286 initial data that may indicate current prescription patterns in the UK sheep industry. Further studies  
287 that incorporate true random sampling would be of value.

288 The subset analysis of antibiotic prescriptions per disease process from one practice (24 flocks)  
289 suggested that the pattern of antibiotic usage across the 24 flocks was comparable to the dataset as  
290 a whole in terms of overall usage per flock, relative usage by antibiotic classes and seasonality of  
291 usage. It would therefore seem reasonable to conclude that some useful estimates of the disease  
292 diagnoses underpinning antibiotic usage may be drawn from this subset of data. Principally the  
293 treatment of lameness was the most common reason for the use of antibiotics (mainly  
294 oxytetracycline) in sheep flocks, accounting for approximately 65 % of total mg/PCU. This result is  
295 not surprising given the prevalence of footrot, interdigital dermatitis and contagious ovine digital  
296 dermatitis. However, since important variation between practices in prescribing policies was also

297 identified in this study, it should also be recognised that records from one veterinary practice may  
298 not be representative of practices in general.

299 Prompt parenteral antibiotic treatment (PAT) forms part of the accepted best practice guidelines for  
300 the control of footrot (Kaler et al, 2010) and has been shown to reduce the prevalence of footrot in  
301 flocks. In many upland and hill flocks, where grazing management is more extensive and PAT is not  
302 practical, regular periodic treatment with parenteral antibiotics has also been suggested to be  
303 effective in reducing lameness prevalence (Angell & Duncan, 2015). The authors suggest that some  
304 of the significant variation observed in this study between lowland and hill flocks in the usage of  
305 oxytetracycline may be due to the greater difficulty in adopting PAT protocols for lameness  
306 management in comparison to their lowland counterparts. Infection pressure and risk of clinical  
307 disease may also vary between these hill and lowland farms.

308 Whilst lameness prevalence is referred to widely (J. R. Winter, Kaler, Ferguson, Kilbride, & Green,  
309 2015), there is little published data on the incidence rates of lameness in commercial flocks under  
310 typical management conditions. The extrapolated treatment rate calculated in this study from the  
311 subset of 24 flocks with detailed diagnosis data on each antibiotic product unit is an attempt to use  
312 readily available data to provide a crude estimate of treatment rate as a proxy for disease incidence.  
313 Accepting that the treatment rate measure used makes several key assumptions as detailed  
314 previously, the high median treatment rates of 29.6 cases per 100 ewes per year and wide range  
315 between farms may represent a reasonable benchmark when considering appropriate strategies for  
316 lameness control.

317 Whilst the use of parenteral oxytetracycline would seem most plausibly attributed to its perpetual  
318 use in the control of infectious lameness a small seasonal increase observed in February and March  
319 could be attributed, at least in part, to the prophylactic or metaphylactic use in the control of  
320 *Chlamydophila abortus*. This use of oxytetracycline was estimated in this study at 5% of flocks (table  
321 2) per year and by others as high as 10% of flocks per year (Lovatt et al, unpublished data).

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322 Oral aminoglycosides are licenced for the treatment and/or prophylaxis of enteric *E.coli* infections in  
323 neonatal lambs. The ESVAC methodology for calculating DDDvet and DCDvet values for oral  
324 antibiotics dramatically underestimate the number of individuals and thus the proportion of the  
325 population that are treated. For this reason it seems logical that neonatal antibiotic preparations  
326 should be recorded as a 'per animal' dose rather than as mg/kg body weight. In this study, 49% of  
327 farms were prescribed oral antibiotics. Extrapolating from the UK benchmarked mean rearing  
328 percentage of lambs per ewe (143.5%), the mean and median doses per lamb reared per flock using  
329 oral antibiotics is approximately 0.86 and 0.64 respectively.

330 The most common aminoglycoside antibiotic preparation prescribed in this study is also licenced for  
331 use in piglets. In piglets, the exposure of the developing gastrointestinal flora to antibiotics has been  
332 shown to have enduring effects on the microbiota (Schokker et al, 2015). It is unclear if similar  
333 results would be expected in ruminant species. It has been shown that there is significant variation  
334 in microbiota between calves from different beef herds (Weese & Jelinski, 2017) and early life  
335 exposure of calves to antibiotics was hypothesised as a potential contributory factor. More research  
336 is required to understand the dynamics of the microbiota development in lambs and what affect  
337 peri-natal antibiotic treatment may have on antimicrobial resistance as well as their long term  
338 health.

339 Topical use of antibiotics presents a different but no less important challenge. Topical antibiotic  
340 preparations are excluded from ESVAC DDDvet/DCDvet metrics, however in the sheep and cattle  
341 industries, these products are commonly used both in antibiotic footbaths and also as topical sprays,  
342 primarily for the treatment of pathogens causing lameness. A wide range of soluble antibiotic  
343 products including macrolides, aminoglycosides, lincomycin and fluoroquinolones were prescribed  
344 to a small proportion of flocks (7%). In the authors' experience, these products, licenced for oral  
345 administration to pigs, poultry and calves, are prescribed overwhelmingly for the treatment and  
346 control of lameness caused by CODD. The use of such preparations by this route for treating

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3 347 lameness is a well-established clinical approach for CODD in sheep and the cattle equivalent  
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5 348 condition, digital dermatitis, in the UK and internationally (Laven & Logue, 2006; A. C. Winter,  
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7 349 2011). In the case of CODD in particular, there is no published evidence to support this form of use,  
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9 350 whilst the evidence to support the use of antibiotic footbaths to control of digital dermatitis in cattle  
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11 351 is weak. The lack of an evidence base to guide decisions on dose rate and effective application  
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13 352 protocols raises the possibility that sub-therapeutic dosing may be common in this clinical scenario,  
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15 353 whilst spent footbath solutions are commonly discharged into slurry or the environment. It must be  
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17 354 recognised that in addition to the causative pathogens, a wide variety of other bacterial species on  
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19 355 the foot and in the soil environment will also be exposed as a result of the use of these antibiotic  
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21 356 products in this way. This is an undesirable and potentially imprudent use of antibiotics, which is  
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23 357 difficult to justify unless substantially better welfare outcomes can be demonstrated compared to  
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25 358 targeted treatment with parenteral antibiotics, which is known to be highly efficacious (Duncan et al.  
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27 359 2011, 2012, Angell et al, 2014, Angell & Duncan, 2015). CODD is estimated to affect approximately  
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29 360 35% of UK flocks (Angell et al, 2014) Assuming a similar prevalence of CODD for the flocks in this  
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31 361 study, it can be inferred that the majority of CODD affected flocks are not using antibiotic footbaths  
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33 362 to control this disease on a regular basis.  
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38 363 It cannot be assumed that low antibiotic usage correlates with low disease or good welfare and  
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40 364 there is a great danger in conflating the two measures. Low, targeted usage of antibiotics in all  
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42 365 veterinary species is desirable but this must be balanced with concern for animal welfare and  
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44 366 sustainable productivity. This study has demonstrated significant variation in antibiotic usage  
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46 367 between farms and between veterinary practices. Further research is required to understand the  
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48 368 biological, managerial and physiological drivers of antibiotic prescription and use among sheep  
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50 369 farmers and their prescribing veterinary surgeons in order to achieve a sustainable reduction in  
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52 370 antibiotic use.  
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Figures

Figure 1 Distribution of antibiotic usage in total mg/PCU from 207 individual sheep flocks in England, Wales and Scotland compiled from prescribing records of eight veterinary practices over a 12 month period from 1st August 2015 to 31st July 2016.

Figure 2 Percentage of total antibiotic usage mg/PCU per month for all flocks by antibiotic class.

Figure 3 Distribution of flock antibiotic usage in mg/PCU by farm stratification. Box indicates the interquartile range. Whiskers indicate upper and lower quartiles excluding outliers calculated as those > 1.5 IQR from Q1/Q2 or Q3/Q4 boundary. Median is identified by horizontal line, mean is identified by black diamond.

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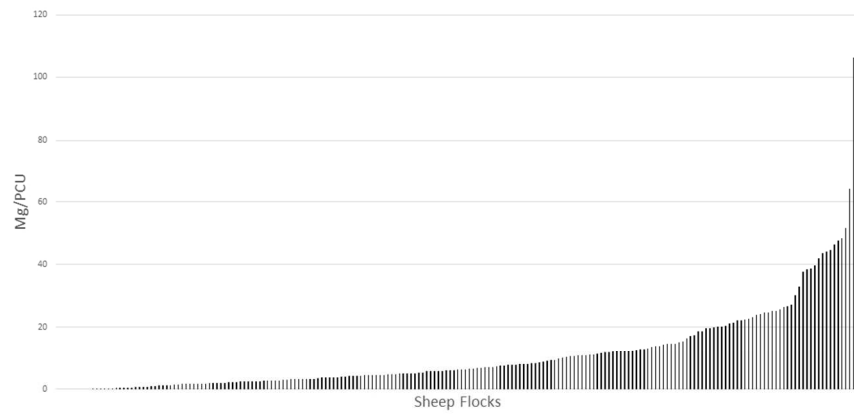


Figure 1 Distribution of antibiotic usage in total mg/PCU from 207 individual sheep flocks in England, Wales and Scotland compiled from prescribing records of eight veterinary practices over a 12 month period from 1<sup>st</sup> August 2015 to 31<sup>st</sup> July 2016.

338x190mm (96 x 96 DPI)

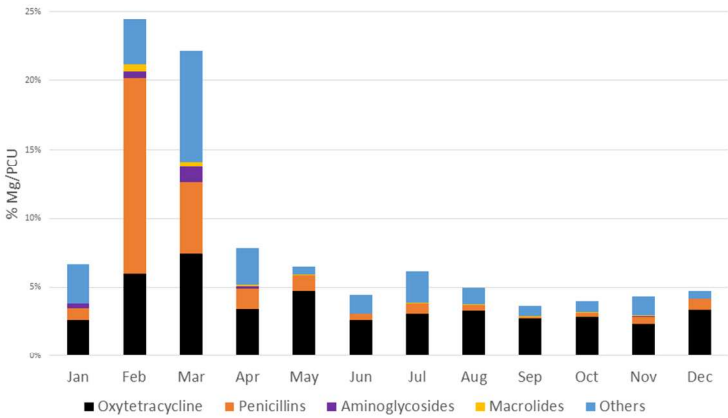


Figure 2 Percentage of total antibiotic usage mg/PCU per month for all flocks by antibiotic class.

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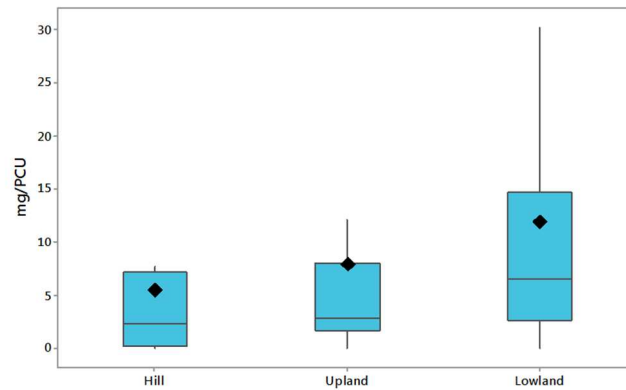


Figure 3 Distribution of flock antibiotic usage in mg/PCU by farm stratification. Box indicates the interquartile range. Whiskers indicate upper and lower quartiles excluding outliers calculated as those  $> 1.5$  IQR from Q1/Q2 or Q3/Q4 boundary. Median is identified by horizontal line, mean is identified by black diamond.

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